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REFERENCES

1. Heckbert SR, Post W, Pearson GD, et al. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multiethnic Study of Atherosclerosis. J Am Coll Cardiol 2006;48:2285–92.

2. Lieb W, Xanthakis V, Sullivan LM, et al. Longitudinal tracking of left ventricular mass over the adult life course: clinical correlates of short- and long-term change in the Framingham Offspring Study. Circulation 2009;119:3085–92.

3. Gidding SS, Liu K, Colangelo LA, et al. Longitudinal determinants of left ventricular mass and geometry: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Circ Cardiovasc Imaging 2013;6:769–75.

Atrial Fibrosis

An Illusion or a True Key to Successful Ablation of Atrial Fibrillation?

We read with great interest the article by Kottkamp et al. (1). We agree that atrial fibrosis may play an important role in the maintenance of atrial fibrillation (AF). However, we would like to stress a few points that seem to us important.

First, causal relationship between atrial fibrosis and AF has not been clearly confirmed. In fact, recent evidence indicates that while the atrial fibrosis naturally accompanies structural heart disease it is not directly linked to AF *per se* (2). There is also no direct evidence that AF can promote atrial fibrosis in humans. Clearly, the pathophysiology of AF extends far beyond the mere concept of atrial fibrosis.

Second, although magnetic resonance imaging with late gadolinium enhancement (LGE) has been extensively validated for visualization of a distinct post-infarction scar in the left ventricle, the technique has not been histologically validated for detection of predominantly diffuse pre-ablation fibrosis in the atria by any systematic study in humans or in an animal experiment. Similarly, there is no histological proof that low endocardial voltage in the atria reflects solely fibrosis. Therefore, we believe that neither low endocardial voltage nor the LGE may be interpreted as atrial fibrosis without precautious.

Our own data show no correlation between the extent of pre-ablation left atrial LGE and other characteristics of the atrial remodeling such as volume, phasic function, or bipolar voltage. Most importantly, in our experience the extent of left atrial LGE does not predict AF recurrence after ablation (3).

Thus, we feel that more solid experimental and clinical evidence is needed before clinical application of the proposed approaches to ablation of AF that are based on visualization and modification of the presumed "atrial fibrosis."

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REFERENCES

1. Kottkamp H, Bender R, Berg J. Catheter ablation of atrial fibrillation: how to modify the substrate? J Am Coll Cardiol 2015;65:196–206.

2. de Oliveira IM, Oliveira BD, Scanavacca MI, Gutierrez PS. Fibrosis, myocardial crossings, disconnections, abrupt turns, and epicardial reflections: do they play an actual role in human permanent atrial fibrillation? A controlled necropsy study. Cardiovasc Pathol 2013;22:65–9.

3. Sramko M, Peichl P, Wichterle D, et al. Clinical value of assessment of left atrial late gadolinium enhancement in patients undergoing ablation of atrial fibrillation. Int J Cardiol 2015;179:351–7.

REPLY: Atrial Fibrosis

An Illusion or a True Key to Successful Ablation of Atrial Fibrillation?

We thank Drs. Sramko and Kautzner for their interest in our manuscript (1). The success rates of current stepwise ablation approaches adding the placement

of "traditional" linear lines and electrogram-based ablation after pulmonary vein (PV) isolation are disappointingly low and indicate the need for new substrate-targeted ablation strategies for atrial fibrillation (AF) therapy.

Drs. Sramko and Kautzner commented on the complex pathophysiology of AF. In fact, there is general agreement about the complexity of the roles of triggers (especially but not exclusively from the PVs), of the substrate (including atrial fibrosis), and of a variety of modulators/modifiers (including hypertension, obesity, and other cardiac risk factors, but also inflammation, cancer, and other conditions). We have analyzed data from intraoperatively obtained specimen, post-mortem autopsy findings, electroanatomic voltage mapping (EAVM) studies, and delayed enhancement (DE) magnetic resonance imaging (MRI) investigations, all of them supporting the role of atrial fibrosis for the human AF substrate, but questioning "traditional wisdom" such as AF begets AF and also the etiological role of age (2,3). Recently, atrial fibrosis was described to appear to be "a common endpoint of a wide range of AF-promoting conditions" (4).

Drs. Sramko and Kautzner commented in addition on the role of DE MRI as well as EAVM as imaging/mapping techniques or surrogates for atrial fibrosis. With respect to DE MRI, we have indicated in our manuscript that "this modality requires extensive MRI experience, and its reproducibility is still under investigation in other groups" (1). In general, new strategies and technologies that are introduced into clinical practice always have limitations. In order to appreciate the current limitations of our proposed new techniques, we included a "limitations" paragraph, which is indeed the longest in our whole manuscript (1). However, despite all limitations inherent to new techniques/technologies, we see the future role for our proposed strategies including the "box isolation of fibrotic areas," and several clinical studies are currently being performed already.

Overall, although it seems that we look from different angles, we indeed appreciate all comments from Drs. Sramko and Kautzner because an open and respectful discussion helps to further develop the promising field of substrate modification in AF ablation for our patients.

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REFERENCES

1. Kottkamp H, Bender R, Berg J. Catheter ablation of atrial fibrillation: how to modify the substrate? J Am Coll Cardiol 2015;65:196–206.

2. Kottkamp H. Human atrial fibrillation substrate: towards a specific fibrotic atrial cardiomyopathy. Eur Heart J 2013;34:2731–8.

3. Kottkamp H. Fibrotic atrial cardiomyopathy: a specific disease/syndrome supplying substrates for atrial fibrillation, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications. J Cardiovasc Electrophysiol 2012;23:797–9.

4. Nattel S, Harada M. Atrial remodeling and atrial fibrillation. J Am Coll Cardiol 2014;63:2335–45.

Atherosclerotic Burden

Complex Interplay of Anatomic, Physiologic, and Outcome Data

The review by Arbab-Zadeh and Fuster advocates for the assessment of atherosclerotic disease burden as opposed to individual plaque vulnerability in patients at risk for cardiac events. It also cites a post hoc analysis of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, stating that angiographic data (clearly not the optimal way to assess atherosclerotic burden) are superior to myocardial ischemia testing in predicting outcome. So is the predictive value of ischemia assessment simply a reflection of atherosclerotic burden? The results of combined studies for disease burden, ischemia, and outcomes in different patient populations tend mostly to disagree.

A study by Schenker et al. (1) evaluated 695 consecutive intermediate-risk patients undergoing combined positron emission tomography perfusion imaging and coronary calcium scoring. Patients with ischemia carried a higher event rate at all levels of coronary calcium. In another study of 541 patients with suspected coronary disease undergoing coronary computed tomography (CT) angiography and single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), anatomic and functional information was synergistic (2). MPI information remained significant in multivariate models and the event rates between patients with none or mild coronary stenosis and abnormal MPI and